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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,625	07/16/2001	Peter Kufer	009848-0276371	3114

27500 7590 10/27/2005

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EXAMINER

YU, MISOOK

ART UNIT PAPER NUMBER

1642

DATE MAILED: 10/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

09/744,625

Applicant(s)

KUFER ET AL.

Examiner

MISOOK YU, Ph.D.

Art Unit

1642

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 May 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 23 May 2005. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 112, second paragraph.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: 1,2,4,6,7,19-23 and 26.
Claim(s) withdrawn from consideration: 3,5,8-18,24,25 and 27-41.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____.
13. ☒ Other: the non-final Office action mailed on 8/10/2005 is vacated.

Misook Yu 10/25/2005



Continuation of 11. does NOT place the application in condition for allowance because: The rejection of record are maintained for the following reasons: Applicant argues that the prior art of record does not teach that the product is not expressed in and secreted by a mammalian host cell as the claim 1 as amended requires. This argument is fully considered but found unpersuasive because the how the claimed product is made is not given patentable weight. The claimed invention is drawn to product per se.


As stated before in the previous Office actions, Muller et al., teach a heterodimer comprising two monomers, wherein the first monomer comprises CH1 domain linked via C-and/or-N-terminal to two functional domains i.e. VH and VL functional domains of anti-EGF-R scFv fragment, and the second monomer comprises CL1 linked via C-and/or-N-terminal to two other functional domains i.e. VH and VL functional domains of anti-CD2 scFv fragment (total four functional domains in the multifunctional compound, as specified instant claim 4), wherein the two different polypeptides (i.e. anti-EGF-R scFv fragment and anti-CD2 scFv fragment) lack an intrinsic affinity for one another, wherein the heterodimer is formed by a disulfide bond between the CH1 domain of the first monomer and the CL domain of the second monomer (note Fig. 1, the heading "Materials and methods" at pages 259-261, and Fig. 2), wherein at least one of the two monomers is to be able to bind a tumor associated antigen (note page 259, right column, 1st paragraph, where it teaches "mini-antibodies capable of binding to the EGR receptor" that is "overexpressed by a wide range of tumors"), wherein said CL1 domain is from the kappa type chain of an immunoglobulin (note line 8 under the sub-heading "plasmid construction" at page 259, left column), wherein the CH1 domain or the CL domain is connected to the different four functional domains, at least two of the four functional domains having a ligand function to a EGF receptor (note page 259, 1st paragraph), namely by a polypeptide linker, or an Ig-hinge region, more specifically an IgG hinge region (note line 8 under the sub-heading "plasmid construction" at page 259, left column and Fig. 1B), wherein the CH1 domain is linked to a histidine tag (note line 2 from bottom of page 259, left column under the sub-heading "plasmid construction" and Fig. 1B). The recitation of "expressed in and secreted by a mammalian host cell" in the amended claim 1 does not limit either the function and/or structure of the claimed multifunctional compound. In other words, the instant claim 1 is a product by process claim. As stated in the previous Office actions, the supporting document, WO 97/01580 demonstrates that a multifunctional compound can be made in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains before the effective filing date of the instant application. 97/01580 at page 16 especially lines 16 "a mammalian" host cell can be used to produce an engineered fully functional heterodimer antibody, and also teach at page 18 especially lines 4-20 a secretion signal that could be used in a mammalian expression system. Thus, the claimed multifunctional compound could be producible in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains. The Office emphasizes that WO 97/01580 is not cited to explain the structural limitation of the claimed multifunctional compound.

As for 103 (a) rejection of record, applicant argues that Muller et al., do not teach all of the limitation of claims for the reasons given traversing 102 (b) rejection above. However, Muller et al., stand as an 102 (b) art for the reasons given above.

As stated above in the rejection of 102(b), and also in the previous Office action, Muller et al., teach a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide with all the structural limitations of claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26. Muller et al., at the last sentence under the heading "Introduction" also teach why one of ordinary skill would be motivated to use a human sequence i.e. to reduce immunogenicity in a human subject. Muller et al., do not specifically teach "the upper hinge region of human IgG3".

However, Pluckthun and Pack teach at page 89, left column, 1st paragraph "the use of hinge regions creates a spacing, hinge bending and rotational freedom of the associated scFv fragments, similar to the Fv-arms of a complete antibody...but with a fraction of its molecular weight. This was achieved by not adding the dimerization handle directly to the scFv fragment, but rather separated by the upper hinge from murine or human IgG3, known to lead to a flexible arrangements of domains". Further, Pluckthun and Pack teach at the paragraph bridging pages 95-96 that a human IgG hinge region has been used for therapeutic application, which requires reduced "immunogenicity" in a human clinical application.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute the linkers of Muller et al., with the upper hinge region of human IgG3 taught by Pluckthun and Pack, to make a multifunctional compound. This would have been accomplished with a reasonable expectation of success since combination of Muller et al., (Jan. 1998) and Pluckthun and Pack (1997) teach how to make each elements of the claimed invention. One of ordinary skill in the art would have been motivated to make and use the claimed multifunctional compound using the upper hinge region of human IgG3 as the linker because Pluckthun and Pack teach that the upper hinge region of human IgG3 is good for reducing immunogenicity in a human patient and the human IgG3 is also good for its flexibility. .


MISOOK YU
PATENT EXAMINER